

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Prospective Observational Study of Mobile App-Based Patient-Reported Outcomes in Advanced Breast Cancer in Asia
Protocol number	A5481109
Protocol version identifier	Version 0.8
Date of last version of protocol	MARCH 2018
EU Post Authorisation Study (PAS) register number	Study Not Registered
Active substance	Palbociclib (L01XE33)
Medicinal product	Palbociclib (IBRANCE)
Research question and objectives	The primary objectives are to assess and describe clinical and patient-reported outcomes (PROs) in women with locally advanced/unresectable or metastatic (ABC/mBC) HR+/HER2– breast cancer receiving palbociclib in combination with an aromatase inhibitor or fulvestrant as per product label.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	advanced breast cancer
AE	adverse event
AEM	adverse event monitoring
CES-D-10	Center for Epidemiological Studies Depression Scale
eCRF	electronic case report form
CRF	case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ER	estrogen receptor
ER+	estrogen receptor positive
HER2	human epidermal growth factor receptor 2
HER2–	human epidermal growth factor receptor 2 negative
HR	hormone receptor
HR+	hormone receptor positive
HRQOL	health-related quality of life
IRB	institutional review board
mBC	metastatic breast cancer
NIS	non-interventional study
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SF-12	12-Item Short Form Health Survey

2. RESPONSIBLE PARTIES

2.1. Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Justin Binko, PhD	Snr Regional Medical Manager	Pfizer Australia	Pfizer, NSW
Mahmood Alam, MBBS	Regional Medical Lead	Pfizer Australia	Pfizer, NSW
Kaylene Lilly	Senior Project Leader	PAREXEL International Pty Ltd	PAREXEL, Australia
Sean Chang	Manager Biostatistics	PAREXEL International Pty Ltd	PAREXEL, Taiwan
Scott Bowles	Group Account Director	InTouch Solutions	New York, NY

3. ABSTRACT

Study Title: Prospective Observational Study of Mobile App-Based Patient-Reported Outcomes in Advanced Breast Cancer in patients being treated with Palbociclib in Asia

Protocol Version and Date: Version 0.5 March 2018

Rationale and Background: Palbociclib (palbociclib) is a new oral agent developed by Pfizer for the treatment of advanced hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer in postmenopausal women.

To date, there have been few studies evaluating the day-to-day effects of advanced breast cancer (ABC) or metastatic breast cancer (mBC) and its treatment on patients in a real-world setting, and information about the effects of treatment-induced neutropenia on patients' daily functioning outside the context of clinical trials is particularly lacking. To contribute new information about patients' day-to-day Patient Reported Outcomes (PROs), Pfizer has endeavored to develop a smartphone-based mobile application to collect patient-reported data on outcomes associated with the disease and its treatment in a real-world setting in selected countries in Asia.

Research question and objectives: To assess clinical outcomes and PROs in women with locally advanced/unresectable or metastatic (ABC/mBC) HR+/HER2– breast cancer receiving palbociclib in combination with an aromatase inhibitor or fulvestrant as per local country product label.

Study design: Prospective, non-interventional, multicenter study of patients initiating treatment for HR+, HER2– advanced or metastatic breast cancer in selected countries in Asia.

Population: Up to 300 women diagnosed with HR+, HER2– ABC or mBC will be enrolled for the purpose of describing the experiences of palbociclib in combination with either an aromatase inhibitor or fulvestrant.

Patients initiating palbociclib treatment:

- Up to 300 women with HR+/HER2– ABC/mBC who are initiated on:
 - palbociclib + an aromatase inhibitor as initial endocrine-based therapy for ABC or mBC per product label;
 - or
 - palbociclib + fulvestrant for patients with disease progression following endocrine therapy for ABC or mBC per product label.

Variables: Detailed definitions of variables that will be collected or derived for statistical analyses and summaries will be included in the Statistical Analysis Plan (SAP).

Data sources: Study data will be collected via a baseline site questionnaire; PRO questions via mobile application at daily, weekly, and cycle-based intervals; and patient medical information from medical records into an eCRF at baseline through to the end of the follow-up period. There are no protocol-mandated tests, procedures, or clinic visits for this study. All data collection for this study will occur over a 12-month period (from the first patient's first visit to the last patient's end of follow-up assessment), assuming a 6-month enrollment period with a 6-month follow-up period.

Study size: Up to 300 women diagnosed with HR+/HER2– ABC or mBC will be enrolled across multiple centers in 4 selected countries in Asia. Any woman who meets the eligibility criteria will be invited to participate in the study. Eligibility will be assessed prior to enrollment during a scheduled visit.

Data analysis: Analyses will generally be descriptive in nature and will be conducted using SAS statistical software (version 9.3 or higher). All variables will be summarized descriptively through tabular displays of mean, median, ranges, and standard deviations of continuous variables and frequency distributions of categorical variables. Exploratory analyses may be conducted to examine associations and/or other research questions (eg time-to-first-neutropenia using Kaplan-Meier methods). No formal hypothesis testing is planned. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP.

4. AMENDMENTS AND UPDATES

5. MILESTONES

Milestone	Planned date
Start of data collection	May 2018
End of data collection	May 2019
Registration in the EU PAS register	March 2018 - TBD
Database lock	May 2019
Study report addendum	August 2019

6. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer among women in the United States (US), with an estimated 246,660 new cases occurring in 2016 ([Siegel et al., 2016](#)). Although the 5-year survival rates are high among patients diagnosed with earlier-stage breast cancer, only 22% of patients with advanced breast cancer survive for 5 years after their diagnosis ([American Cancer Society, 2014](#)).

In Asia, the incidence of breast cancer is 26 per 100,000 individuals, the mortality rate is 9.5 per 100,000 individuals. In China, the incidence of breast cancer is 21.6 per 100,000 individuals, the mortality rate is 5.7 per 100,000 individuals. Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still only approximately 18-24 months and the medical need for more active agents in this clinical setting remains very high. Palbociclib (palbociclib) is a new oral agent developed by Pfizer for the treatment of advanced hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer in postmenopausal women. In a phase 2 trial, PALOMA-1, women with advanced ER+/HER2- breast cancer treated with palbociclib in combination with letrozole as initial endocrine treatment for their advanced disease had a doubling of progression-free survival (PFS) duration compared to patients receiving letrozole alone (median PFS: 20.2 months [95% CI 13.8-27.5] vs. 10.2 months [95% CI 5.7-12.6], respectively [hazard ratio 0.488, 95% CI 0.319-0.748, one-sided p = 0.0004]) ([Finn et al., 2015](#)). The most common grade 3 or 4 adverse event (AE) was neutropenia (54% in the palbociclib plus letrozole arm vs 1% in the letrozole arm), but no case of febrile neutropenia or neutropenia-related infection was reported during the study. PALOMA-2 is a phase 3 randomized trial of palbociclib plus letrozole versus letrozole alone in 666 postmenopausal women with ER+/HER2- advanced breast cancer who had no prior systemic therapy for advanced disease. The median PFS was 24.8 months in the palbociclib plus letrozole arm compared with 14.5 months in the letrozole alone arm (hazard ratio 0.58 [95% CI 0.46-0.72], p < 0.000001). Neutropenia of any grade

occurred in 79.5% of patients in the combination arm (grade 3 in 56.1%; grade 4 in none; febrile neutropenia in 2.5%) versus neutropenia of any grade in 6.3% of those in the letrozole alone arm. Overall survival results from this study have not yet been reported ([Finn et al., 2016](#)). A phase 3 trial, PALOMA-3, assessing women with metastatic HR+/HER2– breast cancer who had progressed on or following endocrine therapy were treated with palbociclib in combination with fulvestrant similarly found prolonged PFS among patients receiving the palbociclib combination compared to the fulvestrant and placebo groups (median PFS: 9.5 months [95% CI 9.2-11.0] vs. 4.6 months [95% CI 3.5-5.6], respectively [hazard ratio 0.46, 95% CI 0.36-0.59, $p < 0.0001$]) ([Cristofanilli et al., 2016](#)). The most common grade 3 or 4 AE was neutropenia (65% in the palbociclib plus fulvestrant arm and 1% in the fulvestrant plus placebo arm), febrile neutropenia was uncommon in both groups (3 patients vs 1 patient, respectively). On March 31, 2017, the FDA approved a supplemental New Drug Application (sNDA) for palbociclib based on the results from the confirmatory Phase 3 trial PALOMA-2. The FDA action converts the accelerated approval of palbociclib to regular approval and broadens the range of anti-hormonal therapy that may be administered with palbociclib. palbociclib now is indicated in combination with an aromatase inhibitor, expanding on its earlier indication in combination with letrozole, as initial endocrine based therapy in postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer ([Pfizer, 2017](#)).

To date, there have been few studies evaluating the day-to-day effects of advanced breast cancer (ABC) or metastatic breast cancer (mBC) and its treatment on patients in a real-world setting, and information about the effects of treatment-induced neutropenia on patients' daily functioning outside the context of clinical trials is particularly lacking. To contribute new information about patients' day-to-day PROs, Pfizer has endeavored to develop a smartphone-based mobile application to collect patient-reported data on outcomes associated with the disease and its treatment in a real-world setting. Information will also be collected on a case report form (eCRF) to describe the occurrence of neutropenia among patients being treated with ABC or mBC in this study and to assess any association between neutropenia and patient-reported outcomes (PROs).

This non-interventional study (NIS) is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objectives are to assess PROs in women with locally advanced/unresectable or metastatic (ABC/mBC) HR+/HER2– breast cancer receiving palbociclib in combination with an aromatase inhibitor or fulvestrant as per product label.

The following research objectives will be addressed:

- Characterize patients with HR+ HER2– ABC initiating treatment (eg, baseline patient demographics [eg, age, race] and clinical characteristics [eg, comorbidities, tumor stage, histology]).
- Describe changes in patients' general health status as measured by monthly (cycle-based) administration of the 12-Item Short Form Health Survey (SF-12).
- Describe changes in patients' psychological distress as measured by monthly (cycle-based) administration of the Center for Epidemiological Studies Depression Scale (CES-D).
- Describe the extent to which locally advanced or metastatic breast cancer and its treatment are associated with changes in patients' lives in terms of symptoms, PROs and quality of life as measured by daily and weekly administration of targeted patient-reported questionnaires.
- For patients who are employed at baseline, quantify time lost from work in relation to locally advanced or metastatic breast cancer and its treatment.
- Assess patient's satisfaction with treatment.
- Describe dosing administration of palbociclib (eg, reduction, interruptions, duration).
- Describe the incidence, severity, and duration of neutropenia; including (?) time to first neutropenia event.
- Explore the association between PROs, quality of life and neutropenia.

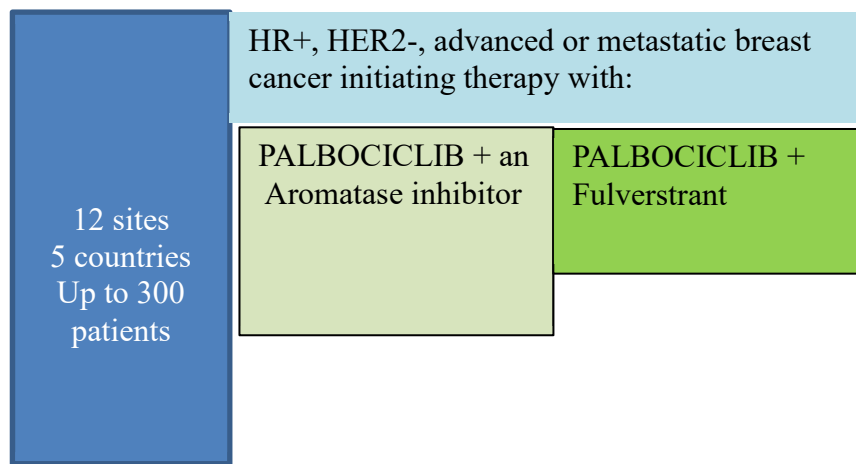
8. RESEARCH METHODS

8.1. Study Design

The study is a prospective, non-interventional, multicenter study of patients initiating treatment for HR+, HER2– advanced or metastatic breast cancer in selected countries in Asia. Participating investigators will screen patients for eligibility, obtain informed consent, and enroll patients meeting the eligibility criteria. Investigators or trained site personnel will then complete a brief eCRF to capture demographic, medical history, and treatment information at enrollment. Interim changes in treatment and clinical outcomes will be recorded for a period of 6 months after enrollment (end-of-study assessment). Enrolled patients will be provided access to and trained on the use of a mobile application to complete baseline, daily, weekly, and cycle-based assessments for a period of 6 months, with an optional additional 6 month for participating patients.

Figure 1 summarizes the overall study design.

Figure 1. Study Design



HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive.

8.2. Setting

Up to 300 women diagnosed with HR+, HER2– ABC or mBC will be enrolled into this non-interventional prospective study across multiple centers in 5 countries in Asia. All patients will be required to have had a diagnosis of mBC or locoregionally ABC not amenable to resection or radiation therapy with curative intent at the time of study entry. Patients could have either a *de novo* diagnosis of advanced or mBC or recur from an earlier stage. Any woman who meets the eligibility criteria will be invited to participate in the study. Eligibility will be assessed prior to enrollment during a scheduled visit.

Participation in this study is not intended to change the routine treatment that patients receive as determined by their prescribing clinicians; all treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician. No additional visits to the clinic will be required for the purposes of the study.

Patients will be included in this study for the purpose of describing the experiences of those on palbociclib in combination with either an aromatase inhibitor or fulverstrant for ABC or mBC as per local label.

Patients initiating palbociclib treatment:

- up to 300 women with HR+/HER2– ABC/mBC who are initiating:
 - palbociclib + an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with ABC or mBC per label;
 - or
 - palbociclib + fulvestrant for patients with disease progression following endocrine therapy for ABC or mBC per label.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Owns or has regular access to an Apple iPhone (version 5.0 or higher with latest software: iOS 9.0 or higher) or Android phone (eg, Nexus or Galaxy with latest software: version 4.4.2 or higher).
1. Adult women (≥ 18 years of age) with diagnosis with advanced or metastatic breast cancer not amenable to resection or radiation therapy with curative intent.
2. Documented evidence of HR+ tumor based on the patient's most recent tumor biopsy.
3. Documented evidence of an HER2– tumor based on the patient's most recent tumor biopsy. HER2– is determined as an immunohistochemistry score of 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio < 2 or, for single probe assessment, a HER2 copy number < 4 .
4. Initiating first, second or third line treatment with one of the following therapies: palbociclib and an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with advanced or metastatic disease as per label, or palbociclib with fulvestrant if the patient has experienced disease progression following endocrine therapy as per label, or other approved therapy as the first treatment for advanced or metastatic breast cancer, or initiating other approved therapy as the second or third treatment for ABC or mBC.
5. Evidence of a personally signed and dated informed consent form document indicating that the patient has been informed of all pertinent aspects of the study.
6. Able to read and understand English or Mandarin Chinese .
7. Willing and able to complete data entry via smart phone (iphone or android) mobile app.

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patient is initiating neoadjuvant systemic therapy.
2. In the judgment of the investigator, the patient's life expectancy is fewer than 3 months at the time of diagnosis of ABC or mBC.
3. The patient is participating in any interventional clinical trial that includes investigational or marketed products. Patients participating in other investigator initiated research or non-interventional studies can be included as long as their standard of care is not altered by the study.
4. The patient is on active treatment for other malignancies other than ABC or mBC.
5. Patient eligibility should be reviewed, documented, and confirmed by an appropriately qualified member of the investigator's study team before patients are enrolled in the study.

8.3. Variables

1. As this is prospective, observational study with information collected, namely through patient medical information collected in the electronic case report form (eCRF) and PROs collected in the mobile application (see Table 2). In addition, the SF-12 and the CES-D-10 will be scored according to each instrument's scoring algorithm. Detailed definitions of additional variables that will be derived from the collected data for the statistical analysis will be included in the Statistical Analysis Plan (SAP) and/or in a separate analytic variable specification document

8.4. Data Sources

Data for this study will be obtained via the following sources:

- **Site Questionnaire:** At the time of site enrollment, site characteristics such as geographic location, size of practice, type of hospital, volume of patients with HR+, HER2- ABC or mBC will be collected via a brief site questionnaire.
- **Patient-Reported Questions via Mobile Application:** All patients will be asked to complete a baseline questionnaire, as well as series of questions at daily, weekly, and/or monthly/cycle-based intervals via a mobile application downloaded onto their smartphones. Two validated PRO instruments will be administered at baseline and monthly; the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D-10) ([Björgvinsson et al., 2013](#); [Irwin et al., 1999](#)) and the 12-Item Short Form Health Survey (SF-12) ([Ware et al., 1996](#); [Jenkinson et al., 1997](#)). Appropriate agreements with the copyright owners will be in place for use in this study. All other items have been developed specifically for this study.

- Patient medical information:** The investigator or authorized medical staff will record clinical and treatment data from patients' medical records into an eCRF at baseline and at the end of the 6-month follow-up period. Site staff may opt to enter data on an ongoing basis (eg, at the time labs are available) rather than wait until the end of the 6 month follow-up. Types of data to be obtained from patient medical records are described in Table 2.

Table 1. Data Collection Schedule

	Data Source	Enrollment	Daily	Weekly	Monthly/ Cycle- Based ^a	End of Study
Site characteristics	Site Staff	X				
Screening	eCRF	X				
Diagnosis of ABC/mBC						
Cancer subtype (HR+/HER2-)						
Treatment being initiated						
Line of therapy						
Informed consent	ICF	X				
Baseline CRF	Medical record/ eCRF					
Disease and treatment history		X				
Comorbid conditions		X				
Performance status		X				
Site of metastases (if present)		X				
Treatment plan at enrollment		X				
Patient-reported questions	Patient					
Age		X				
Race/ethnicity		X				
Education		X				
Employment		X				
Insurance		X				
SF-12		X			X	
CES-D-10		X			X	
Mood (7-point scale)		X	X			

Table 1. Data Collection Schedule

	Data Source	Enrollment	Daily	Weekly	Monthly/ Cycle- Based ^a	End of Study
Pain (0-to-10 NRS)		X	X			
Fatigue (0-to-10 NRS)		X	X			
Use of pain medication			X			
palbociclib use			X			
Impact on mood or emotions				X		
Interference with family life				X		
Interference with social life or activities				X		
Physical activity				X		
Energy or stamina				X		
Productivity				X		
Missed work time (number of hours)				X		
Overall health rating				X		
Neutropenia Awareness				X		
Overall quality of life rating				X		
Overall satisfaction with treatment					X	
eCRF (capturing data for 6 months)^b	Medical record/ eCRF					
Experience with adverse events including neutropenia (eg, type, grade)						
Disease progression						
Reason for discontinuation (if applicable)						
palbociclib-related dose changes and interruptions						
End of Study eCRF	Investigator					

Table 1. Data Collection Schedule

	Data Source	Enrollment	Daily	Weekly	Monthly/ Cycle- Based ^a	End of Study
Study Completion or Early Discontinuation (and reason)						X

ABC = advanced breast cancer; CES-D-10 = 10-item short form of the Center for Epidemiologic Studies Depression Scale; eCRF = electronic case report form; HR+/HER- = hormone receptor-positive/human epidermal growth factor receptor 2-negative; ICF = informed consent form; mBC = metastatic breast cancer; NRS = numerical rating scale; PRO = patient-reported outcome; SF-12 = 12-Item Short Form Health Survey.

- ^a. The optional 12-month extension will be composed in patients who have provided consent for the additional follow-up period.
- ^b. Site personnel may input data into this eCRF on an ongoing basis or complete at the end of follow-up.

8.5. Study Size

The current enrollment target for this non-interventional prospective study is up to 300 women, up to 12 centers and 5 countries in Asia. This is an observational study designed to provide descriptive summary information and is not designed for hypothesis testing. As such, no formal power calculation has been performed. The number of patients was chosen on a practical basis in conjunction with the ability to have reasonable precision around key estimates.

8.6. Data Management

The EDC system that will be used to capture study data at the site (eCRFs) is the DataLabs. The EDC system will be used to collect, monitor, and report clinical data as specified in the protocol. Investigators or authorized staff will enter clinical data directly into the EDC system at enrollment and through the end of study. All data collected via the eCRF will be reviewed by remote data managers for clarity and completeness. Missing or unclear data will be queried according to the data management plan. The database and data management plan, describing data systems used, data sources, data cleaning procedures, and data transfer procedures, will be generated according to approved specifications.

Patient-reported data will be captured using the mobile application designed, programmed, and hosted by InTouch Solutions. These data will be transferred to PAREXEL for analysis as part of the study's primary objectives. Data transfers between PAREXEL and InTouch Solutions will be managed using procedures described in a jointly developed data transfer plan. All data transferred between InTouch Solutions and PAREXEL will be identified only by a subject ID code. Data in both systems will be compared weekly to ensure that participant status is the same in both systems. PAREXEL will combine the InTouch Solutions data and the EDC data at the end of the study.

8.7. Data Analysis

For the purpose of this study, analyses will generally be descriptive in nature and will be conducted using SAS statistical software (version 9.3 or higher). All variables will be

summarized descriptively through tabular displays of mean, median, ranges and standard deviations of continuous variables and frequency distributions of categorical variables. Exploratory analyses may be conducted to examine associations and/or other research questions (eg, time-to-first-neutropenia using Kaplan-Meier methods).

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality Control

Investigators and study coordinators will be trained by PAREXEL and Pfizer with an initial WebEx training session on the protocol, study flow, EDC system (eCRF), mobile app (ePRO), documentation, site responsibilities and expectations, and any applicable study processes. Any questions or discussions that arises pertaining to patient inclusion / exclusion, protocol deviations or violations will be addressed by parexel in discussion with the Pfizer clinician for resolution.

No on-site monitoring visits are planned for this study. Remote data monitoring will be conducted during the study to ensure linkage and integrity between the EDC and PRO systems and to identify missing or unclear data in the EDC system and issue queries to the site for resolution . The remote study monitor and PAREXEL project manager will closely monitor the patient recruitment and data collection to ensure sampling/quota requirements are being met. PAREXEL will also provide oversight of activities, including screening patients, recruiting and obtaining consent from patients, and completing the eCRFs. PAREXEL will maintain regular communication with all sites and will assess progress and site performance and address recruitment or APP use issues as they arise.

8.8.1. Data Transfers, Recording and Document Retention

Data transfers between PAREXEL and InTouch Solutions will be described in a detailed Data Transfer Plan. The transfers made during the course of the study will be used to ensure that participants have the same status (eg, active, completed) in both data systems. At the end of the study, InTouch Solutions will transfer their complete data set to PAREXEL, which will combine the data sets.

Archiving of study documents will be performed according to Pfizer standard operating procedures (SOPs).

8.8.2. Data Quality Assurance

All applicable SOPs and data-cleaning procedures will be followed with the aim of removing errors and inconsistencies in the data that would otherwise affect the analysis, reporting aims, or credibility of the final study report.

For the analysis, all programming written by one study analyst will be reviewed independently by a different analyst with oversight by a senior statistician.

All key study documents—such as the analysis plan, data collection forms, and study reports—will undergo quality-control review, senior scientific review, and editorial review.

The study database will be backed up each night. Access to the EDC system will be by username/password combination only and available only to authorized personnel.

8.9. Limitations of the Research Methods

The sample of participating sites is a convenience sample and is not guaranteed to be representative of all centers that treat patients with ABC/mBC across Asia. Likewise, the patient selection and the diagnostic or monitoring procedures are those applied per the usual treatment paradigm of the treating physician and not dictated by the protocol. Heterogeneous patient populations could make the interpretation of the outcomes difficult.

As with all studies that require patients to self-report outcomes and behavior, completeness and accuracy of reporting can be a concern. Study participants wishing to be seen as responsible patients may over-report compliance. In addition, while patients will be asked to complete the daily questions at a consistent time of day, they will be able to access and complete the daily questions at any point during the 24-hour period.

The data collection methods have been designed to be appropriate and accessible to the study population. Nevertheless, some errors in recording information and some missing information can be anticipated, particularly given the frequency and length of PRO data collection (daily, weekly, and monthly items over a 6-month data collection period).

As this study will collect PRO data through the use of a mobile app, use and knowledge of mobile devices is required to participate, the study population may not be representative of the mBC/ABC population, which may include technology- or mobile device-naïve patients.

In summary, the source data described in this protocol contain the inherent limitation of any current non-interventional, real-world study. These studies have the potential for missing, inaccurate, or incomplete data. These limitations can result in methodological challenges in attributing causality to outcomes. Hence, this study is intended for hypothesis generation as opposed to hypothesis confirmation.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data. Data transferred between PAREXEL and InTouch Solutions will be identifiable only by subject ID number.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study and any changes made during the course of the study must be prospectively approved by both the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The study protocol, the ICF, and the HIPAA authorization form must be approved by an appropriate IRB before the study is initiated at the site. Documentation of this approval must be provided to PAREXEL before the site training visit is conducted. The IRB used must comply with current ICH GCPs.

The investigator's responsibilities regarding IRB are as follows:

- Obtain IRB approval for any protocol amendments and ICF revisions before implementing the changes.
- Provide the IRB with information regarding serious adverse event (SAE) reports regardless of causality during the study as required or requested by their IRB.

- Submit progress reports to the IRB, as required, during the conduct of the study; requesting re-review and approval of the study, as needed.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, the International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, and the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This section describes the management and reporting of AEs/ARs. This section applies to palbociclib in combination with an aromatase inhibitor or fulvestrant as per product label.

The table below summarizes the requirements for recording safety events on the eCRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section “Definitions of safety events”.

Table 2. Requirements for Recording and Reporting Safety Events

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "[Serious Adverse Events](#)" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of palbociclib for HR+/ HER2- ABC / mBC and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation or failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to palbociclib or the partner antihormonal agent (ie, an aromatase inhibitor or fulvestrant) HR+/ HER2- ABC / mBC, the SAE also must be reported to Pfizer Safety.

Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether palbociclib or the partner antihormonal agent for HR+/ HER2- ABC / mBC caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that palbociclib or the partner antihormonal agent for HR+/ HER2- ABC / mBC did not cause the event, this should be clearly documented on the eCRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;

- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios Necessitating Reporting to Pfizer Safety within 24 Hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC (maternal exposure).
2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
3. A male has been exposed, either due to treatment or environmental exposure to palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to palbociclib or other oncologic medicinal products for HR+/ HER2- ABC / mBC in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication Error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
 - An identifiable reporter;
 - A suspect product;
 - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

- Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

- Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.1. Single Reference Safety Document

The local country Prescribing Information for palbociclib (palbociclib) in combination with aromatase inhibitors or fulvestrant will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study. Should SAEs be reported on any non-Pfizer product used in the treatment of mBC/ABC, or the partner antihormonal agent for such a product will be the local countries product information.

The SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study are not part of any planned regulatory submission. The results may be submitted for abstracts and publications. The final CSR will be filed in Pfizer's Global Document Management System upon final study completion.

12. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Individual Country PI's to serve a 7.2. Single reference safety document.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

18. ANNEX 3. ADDITIONAL INFORMATION

Countries' and patient Allocation

5 countries and up to 12 centers will be used for this study with a cap at center of 25 patients (depending on final number of centers selected) to allow equal registration. This can be reviewed based on needs to expand the cap at sites that are recruiting well and compensate for those sites that have a poor enrollment.